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| 10/527,077 | 06/28/2006 | Thomas G. Schlagheck | 448-67 PCT US | 4740 |

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| EXAMINER | |
|---|---|
| MAEWALL, SNIGDHA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,077 | SCHLAGHECK, THOMAS G. | |
| | Examiner | Art Unit | |
| | Snigdha Maewall | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *63-66* is/are pending in the application.

4a) Of the above claim(s) *1-62 and 67-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Receipt of applicants arguments/remarks filed on 12/22/08 is acknowledged.

Claims 1-49 have been cancelled.

Claims 50-62 and 67-76 have been withdrawn

Claims **63-66** are under prosecution.

The rejections/objections not reiterated herein have been withdrawn in view of applicants arguments.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruso et al. "Dextromethorphan, an NMDA-receptor antagoinist enhances the

analgesic properties of morphine" Inflammopharmacology vol. 8, No.2, pp. 161-173, in view of Roswell USP 4,574,080.

Caruso et al. teaches a composition comprising the NMDA receptor antagonist, dextromethorphan in combination with morphine; the components being present in a 1:1 ratio (page 162, first paragraph). Caruso et al. teaches dextromethorphan enhances the analgesic properties of morphine (page 162, first paragraph and page 172, see discussion).

Caruso et al. differs from instant claims insofar as it does not disclose dextromethorphan in an immediate release carrier or morphine in an extended release carrier

Roswell et al. teaches it is advantageous to combine two active substances to obtain a combination effect of improve patient compliance (col. 2, lines 6-8).

Roswell et al. discloses pharmaceutical compositions comprising compositions containing active agents in which one is present in an extended release form and another is present in an immediate release form, wherein the active substance in immediate release form is coated on the surface or the extended release coating (see claim 1). Roswell et al. discloses the extended release form comprises a base material selected from cellulose derivatives, acrylic polymers, vinyl polymers, and other high molecular synthetic polymers (see claims 1, 6 and 12). Roswell teaches suitable active substance used in the extended release and the control release formulations may be found among various therapeutic groups such as analgesics (col. 8, lines 35-49).

Roswell et al. differs insofar as it does not disclose the specific active agents to be dextromethorphan and morphine.

It would have been obvious to have formulated the composition of Caruso in an extended release /immediate release formulation in order to obtain a combination effect (which is taught by primary reference to be the enhancement of the analgesic properties of morphine) or to increase patient compliance, as taught by the secondary reference.

***Response to Arguments***

4. Applicant's arguments filed 12/22/08 have been fully considered but they are not persuasive.

Applicant argues that Roswall et al. is cited for disclosing pharmaceutical compositions containing active agents in which one is present in an extended release form. It is respectfully submitted that one skilled in the art would not find it obvious to combine those references. Moreover, Applicant has provided evidence of unexpected results illustrating the superiority of the claimed composition. It is not at all obvious that better results can be obtained by releasing the dextromethorphan immediately as opposed to having both the opioid and the dextromethorphan as extended release agents. Caruso et al. teaches that dextromethorphan as NMDA receptor antagonist enhances the analgesic properties of morphine. But neither Caruso et al. or Roswall et al. disclose or suggest that loading NMDA receptors with dextromethorphan soon after drug administration and then metering out the opioid analgesic may pharmacologically

increase the enhancing effects of the NMDA receptor antagonist on the analgesic drug such that less dextromethorphan is required to provide the necessary ratio of dextromethorphan to analgesic. This reduces any adverse side affects of dextromethorphan.

Applicant's arguments are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Caruso et al. have been cited for the teachings of a composition comprising the NMDA receptor antagonist, dextromethorphan in combination with morphine; the components being present in a 1:1 ratio (page 162, first paragraph). Caruso et al. teaches dextromethorphan enhances the analgesic properties of morphine (page 162, first paragraph and page 172, see discussion).

Secondary reference has been cited for the teachings that it is advantageous to combine two active substances, either to obtain a combination effect of improve patient compliance (col. 2, lines 6-8). Roswell et al. discloses pharmaceutical compositions comprising compositions containing active agents in which one is present in an extended release form and another is present in an immediate release form, wherein the active substance in immediate release form is coated on the surface or the extended release coating (see claim 1). Various amounts have also been cited in the

prior art. As such optimization of amounts would have been within the purview of a skilled artisan and come to the claimed invention. It should be noted that claims do not recite that adverse side affects of dextromethorphan is reduced and no amount has been cited in claim 63.

Applicants argue that: referring now to Applicant's specification page 11, line 9 to page 12, line 16, it is explained that a 1:1 ratio of morphine to dextromethorphan enhances analgesic effect of morphine. Further increases in the relative amount of detromethorphan, for example to a 1:2 ratio, increases the enhancement even further but may increase the risks of adverse side effects of dextromethorphan. A higher ratio of dextromethorphan to opioid analgesic may be obtained systemically with lower amounts of dextromethorphan, if 100% of the dextromethorphan is immediately released while a portion of the opioid analgesic is released over time. The release of 100% dextromethorphan as an immediate release component (IR) provides greater amounts of dextrornethorphan to morphine in an extended release component (ER) on an absolute ~molar basis at the systemic level, compared to where both drugs are administered as extended release components (ER-ER) as shown in Table 1 (page 12 of the specification). As is apparent from Table 1, there is a 2-fold or more increase in absolute ratio of analgesic to dextromethorphan at the systemic level when equimolar amounts of dextromethorphan IR are administered compared with dextromethorphan ER. Thus, 50% less dextromethorphan IR will achieve, in this example, a minimum 1:1 ratio of dextromethorphan to the analgesic at the systemic level. The lower amount of

dextromethorphan required to provide the needed ration will provide reduced side effects.

Applicants arguments are not persuasive because primary reference has been cited for the ratio which is same as 1:1 ratio that applicant is referring to. Secondary reference has been cited for two actives in extended and immediate release improvements and for patient compliance. As such mere rearrangement of prior arts elements to leading to predictable results is not an illustration of unexpected results. Furthermore no data has been provided by applicants by performing side by side comparison of prior arts release profile versus the claimed invention to show unexpected results. Since the prior art does not recite any antagonist, it is the position of the examiner that teachings of prior art's combination makes the claimed invention obvious.

**5. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore /

Primary Examiner, Art Unit 1612